Clinical trial results:
A multi-center, un-controlled, open-labeled trial of the long-term safety of Velmanase Alfa aftercare
treatment of subjects with alpha-Mannosidosis whom previously participated in velmanase alfa - trials

Summary

EudraCT number	2013-000321-31
Trial protocol	DK PL
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	21 May 2023
First version publication date	21 May 2023

Trial information

Trial identification

Sponsor protocol code	rhLAMAN-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01908725
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2013-000321-31

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com
Scientific contact	Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2022
Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: evaluation of safety of repeated velmanase alfa intravenous (i.v.) treatment of subjects with alpha-mannosidosis; monitoring long-term safety profile including immunogenicity (anti-immunoglobulin (Ig)G) anti-drug antibodies (ADAs)).
Secondary objectives: evaluating long-term efficacy of velmanase alfa on endurance (6-Minute Walk Test (6MWT), 3-Minute Stair Climb Test (3MSCT)), pulmonary function, serum oligosaccharides, hearing, cognitive development (Leiter International Performance Scale - Revised), motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition), quality of life (Childhood Health Assessment Questionnaire (CHAQ), EuroQoL-5 Dimensions 5-Levels Questionnaire), cerebrospinal fluid (CSF) and 24-hour urine oligosaccharides, central nervous system involvement (imaging and CSF biomarkers (tubulin associated unit, neurofilament light and glial fibrillary acidic proteins)), in vivo biological activity and evaluating pharmacokinetics.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and following all other requirements of local laws. Subjects who had enrolled in earlier velmanase alfa trials (rhLAMAN-02/-03/-04 and rhLAMAN-05) were enrolled. Adverse events (AEs) including infusion-related reactions were collected at every visit. Other safety assessments (performed as per the trial flow chart) included laboratory evaluations (haematology, biochemistry, urinalysis, coagulation tests), physical examination, recording of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature), tests for ADAs and neutralising antibodies (every 12 weeks) and serum IgG/IgM/IgA (every 24 weeks). Electrocardiograms (ECGs) and echocardiograms were recorded at a comprehensive evaluation visit (CEV) performed by 7 subjects who had enrolled in earlier trials. At dosing visits, medical personnel continuously observed subjects until 1 hour post-infusion; observation periods were prolonged if required. Medical/surgical history was recorded at screening. Concomitant medications were collected throughout the trial. During the coronavirus disease 2019 (COVID-19) pandemic, a contingency plan was developed for protection of subjects in treatment phase and appropriate mitigation actions were adopted according to local regulations. As onsite visits were on hold, site staff performed weekly phone calls to obtain information on active subject status, AEs and concomitant medications.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	3
Adolescents (12-17 years)	2
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who had completed the rhLAMAN-04 or rhLAMAN-05 trials of velmanase alfa were eligible for inclusion and 8 subjects were enrolled. Efficacy evaluations were performed in Denmark for all subjects. Infusions were performed in Denmark (for subjects based in Norway and the 1 subject based in the UK) and Poland (for subjects based in Poland).

Pre-assignment

Screening details:

An informed consent from subjects/their legally authorised guardians was obtained prior to any trial-related procedures. Inclusion/exclusion criteria were checked, medical/surgical history and concomitant medications and illnesses were collected, demographics were recorded and a serum pregnancy test was performed as applicable.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable, open-label trial.

Arms

Arm title	Enrolled subjects

Arm description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant lysosomal human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Arm type	Experimental
Investigational medicinal product name	Velmanase alfa
Investigational medicinal product code	CHFLMZYM
Other name	Lamzede
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Velmanase alfa was administered as i.v. infusion once weekly at a dose of 1 mg/kg (weight recorded at first dose and every 4 weeks during the trial). An i.v. catheter could be implanted to ease delivery. The IMP is supplied as a sterile freeze-dried product in single use vials containing 10 mg, each to be reconstituted with 5.0 mL sterile water for injection. Stability of the reconstituted product is 24 hours at 5°C±3°C and 10 hours at a maximum of 25°C. The solution should reach room temperature prior to infusion. Vials were prepared as per the volume required for the dose and swirled with slow rotations for 10-15 seconds after reconstitution. The required volume was withdrawn into one or more large-dose syringes and an infusion set with a mounted filter was filled. The maximum infusion rate was 25 ml/hour. The last empty syringe was replaced with a syringe filled with 20 mL isotonic sodium chloride to infuse the product left in the set.

Number of subjects in period 1	Enrolled subjects
Started	8
Completed	7
Not completed	1
Went on aftercare programme at local hospital	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	8	8	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	3	3	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).			
Units: years			
arithmetic mean	16.5		
standard deviation	± 9.5	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	5	5	

Subject analysis sets	
Subject analysis set title	Paediatric subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).	
Subject analysis set title	Adult subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).	

Reporting group values	Paediatric subjects	Adult subjects	
Number of subjects	5	3	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	3	0	
Adolescents (12-17 years)	2	0	
Adults (18-64 years)	0	3	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).			
Units: years			
arithmetic mean	10.4	26.7	
standard deviation	± 4.3	± 5.8	
Gender categorical Units: Subjects			
Female	2	1	
Male	3	2	

End points

End points reporting groups

Reporting group title	Enrolled subjects

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant lysosomal human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Subject analysis set title	Paediatric subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).

Subject analysis set title	Adult subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05).

Primary: Number of subjects with infusion-related reactions (IRRs)

End point title	Number of subjects with infusion-related reactions (IRRs)[1]

End point description:

An adverse drug reaction (ADR) was an AE assessed to be related to study treatment by the Investigator. An IRR was defined as an ADR which occurred during or within 2 hours after the end of the infusion of velmanase alfa and was assessed by the Investigator as being infusion-related. The AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The IRRs were summarised by System Organ Class and Preferred Term (PT) overall and by age group. The number of subjects experiencing events is presented by PT.

End point type	Primary

End point timeframe:

Data for IRRs were collected from enrolment in rhLAMAN-09 until the end of trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As per protocol, data have been presented through listings and when applicable summarised, with no inferential statistics implemented.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8[2]	5[3]	3[4]	
Units: Subject				
Vomiting	1	1	0	
Injection site reaction	1	1	0	
Injection site swelling	1	1	0	
Pyrexia	1	1	0	
Dizziness	1	1	0	
Tremor	1	1	0	
Rash	1	1	0	

Notes:

[2] - 2 enrolled subjects experienced 7 IRRs.

[3] - 2 paediatric subjects experienced 7 IRRs.

[4] - No adult subjects experienced IRRs.

Statistical analyses

No statistical analyses for this end point

Primary: Detection of ADAs

End point title	Detection of ADAs[5]

End point description:

Detection of ADAs was part of the primary objective and a safety endpoint. Blood samples were collected for ADA assessments pre-infusion during the CEV and every 12 weeks during dose visits. For subjects who had received placebo during rhLAMAN-05, the first ADA assessment was considered as treatment baseline but only if captured not more than 7 days after the first study treatment administration. Subjects were considered to be ADA-positive if they were positive at treatment baseline or had an ADA-positive test at least once during rhLAMAN-09. Subjects were considered to be ADA-negative if they had no ADA-positive tests. At treatment baseline, 6 subjects were ADA-negative and 2 subjects were ADA-positive. The number of subjects who were ADA-positive/negative as defined above, is presented.

End point type	Primary

End point timeframe:

At treatment baseline (i.e. prior to first ever dose of velmanase alfa including in previous trials) and during rhLAMAN-09.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As per protocol, data have been presented through listings and when applicable summarised, with no inferential statistics implemented.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Subject				
ADA-positive	7			
ADA-negative	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for serum oligosaccharides

End point title	Absolute change from treatment baseline to time windows for serum oligosaccharides

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. If >1 time point was reported in the same window, the average of all values was considered in the analysis. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 6.388 (2.232), 7.440 (2.207) and 4.633 (0.551) µmol/L, respectively. For 132-204 and 228-372 weeks, no data were available for any subject. For 60-84, 108-132 and 612-636 weeks, data were available for only 1 enrolled subject (therefore data not shown below). Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to time windows from start of treatment (0-12 weeks and 24-weekly intervals

thereafter until end of trial).

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5[6]	3[7]	
Units: µmol/L				
arithmetic mean (standard deviation)				
0-12 weeks	-7.125 (± 1.237)	-7.125 (± 1.237)	0 (± 0)	
12-36 weeks	-4.683 (± 2.120)	-5.525 (± 2.133)	-3.000 (± 0.566)	
36-60 weeks	-5.511 (± 2.239)	-6.175 (± 2.358)	-3.850 (± 0.354)	
84-108 weeks	-5.306 (± 1.593)	-6.663 (± 0.477)	-3.950 (± 0.177)	
204-228 weeks	-7.638 (± 1.043)	-7.638 (± 1.043)	0 (± 0)	
372-396 weeks	-3.500 (± 0.889)	0 (± 0)	-3.000 (± 0.283)	
396-420 weeks	-3.600 (± 0.964)	0 (± 0)	-3.050 (± 0.212)	
420-444 weeks	-3.933 (± 1.531)	0 (± 0)	-3.050 (± 0.071)	
444-468 weeks	-3.433 (± 1.623)	-3.517 (± 2.805)	-3.350 (± 0.071)	
468-492 weeks	-3.867 (± 1.601)	0 (± 0)	-3.050 (± 1.061)	
492-516 weeks	-4.644 (± 2.645)	-5.354 (± 3.106)	-3.225 (± 0.035)	
516-540 weeks	-7.700 (± 0.849)	-7.700 (± 0.849)	0 (± 0)	
540-564 weeks	-7.950 (± 0.778)	-7.950 (± 0.778)	0 (± 0)	
564-588 weeks	-7.900 (± 0.990)	-7.900 (± 0.990)	0 (± 0)	
588-612 weeks	-7.300 (± 0.141)	-7.300 (± 0.141)	0 (± 0)	

Notes:

[6] - Data only available for 1 paediatric subject for weeks 372-444 and 468-492, therefore shown as 0.

[7] - No data available for adult subjects for weeks 0-12, 204-228 and 516-636.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for CSF oligosaccharides

End point title	Absolute change from treatment baseline to the CEV for CSF oligosaccharides

End point description:

The mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 10.900 (3.944), 12.340 (4.474) and 8.500 (0.755) µmol/L, respectively.

End point type	Secondary

End point timeframe:

The CEV was performed a mean of 2.5 years from treatment baseline. Absolute change in CSF oligosaccharide concentration from treatment baseline to the CEV was analysed.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8[8]	5[9]	3[10]	
Units: µmol/L				
arithmetic mean (standard deviation)	-0.729 (± 2.930)	-0.980 (± 3.549)	-0.100 (± 0.141)	

Notes:

[8] - 7 enrolled subjects performed the CEV.

[9] - 5 paediatric subjects performed the CEV.

[10] - 2 adult subjects performed the CEV.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine

End point title	Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine

End point description:

Treatment baseline values were available for 2 subjects who were in the paediatric age group (mean (SD) of 904.500 (239.709) µmol/L).

End point type	Secondary

End point timeframe:

The CEV was performed a mean of 2.5 years from treatment baseline. Absolute change in oligosaccharides in 24-hour urine from treatment baseline to the CEV was analysed.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8[11]	5[12]	3[13]	
Units: µmol/L				
arithmetic mean (standard deviation)	-532.550 (± 70.216)	-532.550 (± 70.216)	0 (± 0)	

Notes:

[11] - Absolute change data only available for 2 subjects (with data at treatment baseline and CEV).

[12] - Absolute change data only available for 2 subjects (who had data at treatment baseline and CEV).

[13] - No absolute change data available as no adult subject had treatment baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for the 6MWT

End point title	Absolute change from treatment baseline to time windows for the 6MWT

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the subsequent visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 444.0 (135.0), 411.8 (143.4) and 497.7 (125.7) metres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[14]	
Units: metre				
arithmetic mean (standard deviation)				
0-6 months	42.7 (± 48.6)	57.0 (± 53.1)	14.0 (± 29.7)	
1 year	19.4 (± 84.5)	31.4 (± 92.4)	-10.5 (± 78.5)	
2 years	44.9 (± 72.1)	64.7 (± 70.1)	-4.5 (± 68.6)	
4 years	41.7 (± 84.4)	62.2 (± 93.5)	-9.5 (± 20.5)	
6 years	46.5 (± 74.9)	79.0 (± 57.5)	-34.8 (± 44.2)	
8 years	43.0 (± 28.4)	43.0 (± 28.4)	0 (± 0)	
10 years	27.0 (± 105.1)	103.5 (± 61.5)	-49.5 (± 77.1)	
12 years	112.5 (± 27.6)	112.5 (± 27.6)	0 (± 0)	

Notes:

[14] - For adult subjects, no data available at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for 3MSCT

End point title	Absolute change from treatment baseline to time windows for 3MSCT

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline results for enrolled, paediatric and adult subjects were 51.92 (16.85), 49.73 (19.05) and 55.56 (15.36) steps/minute, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[15]	
Units: steps/minute				
arithmetic mean (standard deviation)				
0-6 months	0.83 (± 8.24)	-0.17 (± 10.19)	2.83 (± 4.01)	
1 year	3.62 (± 11.25)	5.40 (± 12.35)	-0.83 (± 9.66)	
2 years	5.71 (± 9.98)	8.53 (± 10.64)	-1.33 (± 2.36)	
4 years	7.41 (± 11.74)	9.97 (± 13.08)	1.00 (± 5.19)	
6 years	3.26 (± 12.27)	6.83 (± 12.37)	-5.67 (± 8.25)	
8 years	6.13 (± 15.00)	6.13 (± 15.00)	0 (± 0)	
10 years	-3.17 (± 7.56)	0.83 (± 6.84)	-7.17 (± 7.78)	
12 years	14.67 (± 0.94)	14.67 (± 0.94)	0 (± 0)	

Notes:

[15] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced vital capacity (FVC) in litres

End point title	Absolute change from treatment baseline to time windows for forced vital capacity (FVC) in litres

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.334 (1.041), 1.804 (0.884) and 3.217 (0.600) litres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[16]	
Units: litre(s)				
arithmetic mean (standard deviation)				
0-6 months	0.113 (± 0.430)	-0.008 (± 0.375)	0.355 (± 0.573)	
1 year	0.246 (± 0.525)	0.272 (± 0.636)	0.180 (± 0.156)	
2 years	0.411 (± 0.449)	0.480 (± 0.481)	0.240 (± 0.453)	
4 years	0.604 (± 0.733)	0.644 (± 0.813)	0.505 (± 0.742)	
6 years	0.842 (± 0.941)	0.955 (± 0.966)	0.560 (± 1.167)	
8 years	1.389 (± 1.038)	1.389 (± 1.038)	0 (± 0)	
10 years	0.970 (± 1.098)	1.575 (± 1.266)	0.365 (± 0.742)	
12 years	1.650 (± 0.622)	1.650 (± 0.622)	0 (± 0)	

Notes:

[16] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FVC percent predicted

End point title	Absolute change from treatment baseline to time windows for FVC percent predicted

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 83.5 (22.8)%, 80.1 (25.3)% and 89.0 (21.7)%, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[17]	
Units: percentage				
arithmetic mean (standard deviation)				
0-6 months	-5.6 (± 25.3)	-13.4 (± 26.6)	10.0 (± 18.4)	
1 year	-0.2 (± 25.5)	-2.6 (± 30.5)	6.0 (± 8.5)	
2 years	3.1 (± 22.9)	1.3 (± 26.6)	7.5 (± 16.3)	
4 years	3.0 (± 32.9)	-1.6 (± 37.5)	14.5 (± 22.6)	
6 years	5.3 (± 36.1)	1.2 (± 40.0)	15.8 (± 33.6)	
8 years	15.0 (± 33.5)	15.0 (± 33.5)	0 (± 0)	
10 years	-10.5 (± 30.4)	-17.5 (± 41.7)	-3.5 (± 29.0)	
12 years	9.2 (± 28.0)	9.2 (± 28.0)	0 (± 0)	

Notes:

[17] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres)

End point title	Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres)

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.076 (0.972), 1.608 (0.828) and 2.857 (0.690) litres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[18]	
Units: litre(s)				
arithmetic mean (standard deviation)				
0-6 months	0.302 (± 0.530)	0.113 (± 0.405)	0.585 (± 0.728)	
1 year	0.241 (± 0.468)	0.235 (± 0.474)	0.255 (± 0.643)	
2 years	0.289 (± 0.447)	0.191 (± 0.404)	0.535 (± 0.615)	

4 years	0.662 (± 1.058)	0.651 (± 1.222)	0.690 (± 0.856)	
6 years	0.854 (± 0.902)	0.871 (± 0.869)	0.813 (± 1.361)	
8 years	1.248 (± 0.799)	1.248 (± 0.799)	0 (± 0)	
10 years	1.253 (± 0.939)	1.870 (± 0.354)	0.635 (± 0.997)	
12 years	0.885 (± 0.587)	0.885 (± 0.587)	0 (± 0)	

Notes:

[18] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FEV1 percent predicted

End point title	Absolute change from treatment baseline to time windows for FEV1 percent predicted

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 78.2 (16.7)%, 74.3 (11.8)% and 84.7 (24.4)%, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[19]	
Units: percentage				
arithmetic mean (standard deviation)				
0-6 months	3.1 (± 22.8)	-5.9 (± 21.7)	16.5 (± 23.3)	
1 year	1.4 (± 22.0)	-1.0 (± 24.1)	7.5 (± 21.9)	
2 years	0.3 (± 20.0)	-6.0 (± 17.8)	16.0 (± 21.2)	
4 years	1.0 (± 25.6)	-6.5 (± 23.4)	19.8 (± 27.2)	
6 years	8.8 (± 30.6)	3.1 (± 29.0)	23.0 (± 41.0)	
8 years	14.0 (± 28.5)	14.0 (± 28.5)	0 (± 0)	
10 years	13.3 (± 22.1)	13.5 (± 2.1)	13.0 (± 38.2)	
12 years	-3.3 (± 35.8)	-3.3 (± 35.8)	0 (± 0)	

Notes:

[19] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for peak expiratory flow (PEF)

End point title	Absolute change from treatment baseline to time windows for peak expiratory flow (PEF)

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 4.166 (2.540), 3.032 (1.849) and 6.057 (2.676) litres per second, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[20]	
Units: litres per second				
arithmetic mean (standard deviation)				
0-6 months	1.125 (± 1.492)	0.803 (± 0.702)	1.770 (± 2.899)	
1 year	0.679 (± 1.481)	0.322 (± 1.212)	1.570 (± 2.249)	
2 years	1.269 (± 2.180)	0.394 (± 1.509)	3.455 (± 2.454)	
4 years	1.289 (± 2.592)	0.516 (± 1.781)	3.220 (± 4.144)	
6 years	2.376 (± 2.795)	2.307 (± 1.967)	2.548 (± 5.597)	
8 years	2.919 (± 2.389)	2.919 (± 2.389)	0 (± 0)	
10 years	3.593 (± 2.302)	4.800 (± 2.079)	2.385 (± 2.397)	
12 years	1.360 (± 0.863)	1.360 (± 0.863)	0 (± 0)	

Notes:

[20] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Disability Index

End point title	Absolute change from treatment baseline to time windows for CHAQ Disability Index

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (also in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 1.422 (0.853), 1.350 (1.112) and 1.542 (0.191), respectively. The CHAQ Disability Index is scored 0-3 with higher scores indicating greater disability.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[21]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.104 (± 0.635)	0.000 (± 0.791)	0.313 (± 0.088)	
1 year	-0.116 (± 0.379)	-0.188 (± 0.380)	0.063 (± 0.442)	
2 years	-0.136 (± 0.513)	-0.341 (± 0.425)	0.375 (± 0.354)	
4 years	-0.125 (± 0.784)	-0.325 (± 0.854)	0.375 (± 0.265)	
6 years	0.179 (± 0.890)	0.038 (± 1.049)	0.531 (± 0.044)	
8 years	-0.391 (± 0.531)	-0.391 (± 0.531)	0 (± 0)	
10 years	0.240 (± 0.862)	-0.146 (± 1.267)	0.625 (± 0.177)	
12 years	0.375 (± 0.177)	0.375 (± 0.177)	0 (± 0)	

Notes:

[21] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain

End point title	Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 0.675 (0.496), 0.522 (0.450) and 0.930 (0.546), respectively. The CHAQ VAS Pain is scored 0 (no pain) to 3 (very severe pain).

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[22]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.225 (± 0.286)	0.225 (± 0.367)	0.225 (± 0.064)	
1 year	-0.251 (± 0.567)	-0.159 (± 0.659)	-0.480 (± 0.212)	
2 years	-0.026 (± 0.572)	-0.102 (± 0.681)	0.165 (± 0.106)	
4 years	0.178 (± 0.664)	0.012 (± 0.734)	0.593 (± 0.074)	
6 years	0.467 (± 0.555)	0.267 (± 0.512)	0.968 (± 0.308)	
8 years	0.173 (± 0.573)	0.173 (± 0.573)	0 (± 0)	
10 years	0.660 (± 0.748)	0.750 (± 1.061)	0.570 (± 0.721)	
12 years	0.105 (± 0.827)	0.105 (± 0.827)	0 (± 0)	

Notes:

[22] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ VAS General

End point title	Absolute change from treatment baseline to time windows for CHAQ VAS General

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (also in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 0.668 (0.546), 0.480 (0.603) and 0.980 (0.284), respectively. The CHAQ VAS General is scored 0-3 with higher scores indicating poorer quality of life.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3[23]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.290 (± 0.877)	0.488 (± 1.046)	-0.105 (± 0.318)	
1 year	-0.041 (± 0.827)	-0.093 (± 1.005)	0.090 (± 0.127)	
2 years	-0.129 (± 0.550)	-0.120 (± 0.632)	-0.150 (± 0.467)	
4 years	0.351 (± 0.699)	0.279 (± 0.839)	0.533 (± 0.159)	
6 years	0.403 (± 0.670)	0.339 (± 0.809)	0.563 (± 0.011)	
8 years	0.308 (± 0.385)	0.308 (± 0.385)	0 (± 0)	
10 years	0.585 (± 0.658)	0.750 (± 1.061)	0.420 (± 0.255)	
12 years	0.060 (± 0.212)	0.060 (± 0.212)	0 (± 0)	

Notes:
[23] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from the time of informed consent in rhLAMAN-09, for the duration of the trial.

Adverse event reporting additional description:

All TEAEs were collected from spontaneous, unsolicited reports of subjects, by observation and by routine open questioning.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Enrolled subjects

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the IMP velmanase alfa (recombinant human lysosomal alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Reporting group title	Paediatric subjects

Reporting group description:

Subjects aged <18 years at the time of first ever dose of velmanase alfa.

Reporting group title	Adult subjects

Reporting group description:

Subjects aged ≥18 years at the time of first ever dose of velmanase alfa.

Serious adverse events	Enrolled subjects	Paediatric subjects	Adult subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			

subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Enrolled subjects	Paediatric subjects	Adult subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	5 / 5 (100.00%)	2 / 3 (66.67%)
Vascular disorders			
Extravasation blood			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Cochlea implant			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Ear operation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Endodontic procedure			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Eye operation			

subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hearing aid therapy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Tooth extraction			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Impaired healing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Infusion site swelling			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	3	2	1
Injection site reaction			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Injection site swelling			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Peripheral swelling			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	6 / 8 (75.00%)	5 / 5 (100.00%)	1 / 3 (33.33%)
occurrences (all)	28	24	4
Swelling face			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Multiple allergies			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Seasonal allergy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 8 (50.00%)	4 / 5 (80.00%)	0 / 3 (0.00%)
occurrences (all)	8	8	0
Obstructive airways disorder			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	4	2	2
Rhinorrhoea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			

Aggression			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Psychotic disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Investigations			
Nitrite urine present			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Weight increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
White blood cells urine positive			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Buttock injury			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	4	4	0
Face injury			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	3	1	2
Foot fracture			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hand fracture			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Head injury			

subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Ligament sprain			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	4	2	2
Limb injury			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Post procedural swelling			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Procedural pain			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Scratch			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Skin abrasion			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	6	4	2
Skin wound			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Tooth fracture			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	6	5	1
Wound complication			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	4	4	0

Dysarthria			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	19	19	0
Syncope			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Ear pain			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	6	6	0
Otorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	3
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Eye allergy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Eye pruritus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	3 / 8 (37.50%)	3 / 5 (60.00%)	0 / 3 (0.00%)
occurrences (all)	5	5	0
Duodenitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	8	7	1
Glossitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Inguinal hernia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	3	2	1
Oesophagitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Salivary gland enlargement			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Tooth loss			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0

Toothache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	7 / 8 (87.50%)	5 / 5 (100.00%)	2 / 3 (66.67%)
occurrences (all)	10	8	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Eczema			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Nail bed inflammation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Rash erythematous			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 8 (50.00%)	3 / 5 (60.00%)	1 / 3 (33.33%)
occurrences (all)	5	4	1
Back pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	4	0	4

Intervertebral disc disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Joint swelling			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Abscess oral			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
COVID-19			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Device related infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Ear infection			
subjects affected / exposed	5 / 8 (62.50%)	4 / 5 (80.00%)	1 / 3 (33.33%)
occurrences (all)	18	11	7
Fungal skin infection			

subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	5	2	3
Genital infection fungal			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Laryngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Localised infection			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	5	5	0
Moraxella infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nail bed infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	7 / 8 (87.50%)	5 / 5 (100.00%)	2 / 3 (66.67%)
occurrences (all)	75	66	9
Oral herpes			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Oral infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Parotitis			

subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Pharyngitis			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Pneumonia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	3	2	1
Respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	3	1	2
Sinusitis			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	4	2	2
Subcutaneous abscess			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	4	4	0
Tinea versicolour			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	5	1	4
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2013	This was Amendment Number 1 to Protocol Version 1.0 dated 08 April 2013. The protocol was amended to allow inclusion of 2 subjects based in Norway who had participated in the Phase 3 trial (rhLAMAN-05). It had not been possible to identify a physician and a clinical department in Norway willing to continue treatment of these subjects; the amendment allowed these subjects to continue treatment at the clinical trial site in Denmark.
23 December 2013	This was Amendment Number 2 to Protocol Version 1.0 dated 08 April 2013. The protocol was amended to allow inclusion of 1 subject based in the United Kingdom who had participated in the Phase 3 trial (rhLAMAN-05). The local hospital was reluctant to continue treatment of this subject, the amendment allowed this subject to continue treatment at the clinical trial site in Denmark.
07 January 2015	This was Amendment Number 3 to Protocol Version 1.0 dated 08 April 2013. The trial objectives were modified to include evaluation of efficacy of repeated velmanase alfa i.v. treatment of subjects and an additional CEV was added to evaluate additional efficacy parameters and safety laboratory assessments. The secondary efficacy objectives added were: evaluation of impact of long-term treatment with velmanase alfa upon serum oligosaccharides, endurance (3MSCT, 6MWT), pulmonary function, motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition [BOT-2]), hearing, cognitive development (Leiter International Performance Scale - Revised), central nervous system involvement (only in subjects who had participated in rhLAMAN-02 and had baseline assessments for the imaging studies), biomarkers and oligosaccharides in CSF and oligosaccharide clearance in urine and quality of life (questionnaires). Assessment of in vivo biological activity in plasma and pharmacokinetic analysis were added to secondary objectives. Additional safety assessments added at the CEV included haematology, coagulation tests, biochemistry, serum IgG/IgA/IgM, anti-nuclear antibodies, ADAs, urinalysis, 12-lead electrocardiogram and echocardiogram. Assessment of changes in social and leisure skills was also planned during the CEV. An End of Comprehensive Evaluation Visit was also added. An interim analysis of CEV data was added.
20 May 2016	In Protocol Version 2.0 dated 15 April 2016, as well as the above-mentioned amendments, the duration of the trial was extended from 3 to 6 years (and additional yearly evaluation visits included). The laboratory analysing blood samples for ADAs was updated. A Port-a-Cath could be inserted at Investigator's discretion to ease the delivery of velmanase alfa and other i.v. procedures during the trial.
19 April 2017	Protocol Version 3.0 dated 12 January 2017 reflected the change in Sponsor (from Zymenex to Chiesi) and in the name of the study treatment (from Lamazym to velmanase alfa). The primary objective (evaluating the safety of repeated velmanase alfa i.v. treatment in subjects with alpha-mannosidosis) was updated to specify that this included monitoring of the long-term safety profile, including immunogenicity (ADAs), throughout the trial. The maximum infusion duration was updated from 45 ml/hour to 22.5 ml/hour. The laboratory analysing IgG NAbs in seropositive subjects was updated. A CRO (Cromsource) was appointed to submit clinical trial documentation to the relevant authorities, and to monitor the investigational sites.
05 January 2018	In Protocol Version 4.0 dated 06 June 2017, Poland was included as a second country to allow subjects based in Poland to have infusions in their country. In addition, a time window of ±2 months was included for the yearly evaluations.

24 May 2019	In Protocol Version 5.0 dated 05 March 2019, the duration of the trial was extended to September 2020 to ensure aftercare for subjects until velmanase alfa was available on the market. Collection of additional blood samples for research was included to develop a bioanalytical assay for the evaluation of the oligosaccharides content in the mononuclear cells. An additional evaluation visit was included to be performed before the subject left the trial.
01 May 2020	In Protocol Version 6.0 dated 26 September 2019, the duration of the trial was extended to September 2022 (and additional yearly evaluation visits included) to ensure aftercare for subjects until velmanase alfa was available on the market. The BOT-2 assessment was added at yearly evaluations (previously only at the CEV) and collection of serum oligosaccharides at dose visits every 24 weeks and yearly evaluations (previously only at the CEV). Additional laboratory tests (haematology and biochemistry pre-infusion at yearly evaluations and IgG/IgM/IgA pre-infusion at dose visits every 24 weeks) and the corresponding safety endpoint of clinical laboratory parameters was added. It was specified that an IRR was an ADR that occurred during or within 2 hours after the end of infusion of velmanase alfa (previously defined as ADRs that occurred during or after the infusion of velmanase alfa). The acceptable contraceptive methods for women of childbearing potential were specified in the exclusion criteria. The laboratories for oligosaccharide testing were updated. The hosting of the electronic data capture system was transferred to a new provider. A centre in Italy was included for infusions due to the potential inclusion of an Italian subject who had participated in the Phase 2 trial (rhLAMAN-08). Protocol Version 1.0 Italy dated 07 November 2019 was applicable only for Italy and was modified on the basis of general Version 6.0. Of note, the Italian subject was not enrolled in the trial as the subject was treated in the commercial setting.
26 October 2021	Protocol Version 7.0 dated 25 May 2021, included the possibility of permitting subjects based in Norway to have infusions in their country of living. Additional blood samples were requested to further investigate the immunological response of subjects to vaccines (poliovirus, diphtheria toxin, tetanus toxin, pneumococcal polysaccharide, and Hemophilus influenzae type b). The IgE testing process in connection with IRRs was clarified. The possibility to use the serum samples remaining after IgG antibody analyses, upon subjects' consent, for additional research was added. Yearly evaluation time windows were updated from ±2 months to never <7 months apart (ideal interval was 12 months). The infusion rate was updated from a maximum of 22.5 ml/hour to a maximum of 25 ml/hour to align with the summary of product characteristics. Pregnancy was added as a reason for subject withdrawal, and inclusion of follow-up in case of pregnancy. The interim analysis of CEV data was deleted. The laboratory analysing IgG NAbs in seropositive subjects was updated and the new database and application (Viedoc) in place was specified. The possibility to include the Italian subject from Phase 2 trial (rhLAMAN-08) was deleted as this subject would now be treated in the commercial setting.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported